-- 6. A method to screen for drug candidates useful for treating humans with atherosclerosis, SVAS or essential hypertension or preventing the occurrence of atherosclerosis in humans said method comprising measuring activity of elastase in the presence of drugs wherein said drugs which inhibit elastase are said drug candidates. --

Q3

-- 9. A method to screen for a drug candidate useful for treating atherosclerosis, hypertension or SVAS in a human, said method comprising treating an *ELN* +/- [organisms] mouse or human or *ELN* +/- mouse or human cells with drugs and measuring synthesis of elastin RNA wherein a drug which increases synthesis of elastin RNA in said organisms or in said cells is said drug candidate. --

Sub D4

Q4

REMARKS

Restriction Requirement

In response to the Restriction Requirement imposed by the Office Action mailed 17 November 1999, Applicants have canceled the nonelected claims (claims 7-8 and 11-14). Applicants reserve the right to refile these claims as part of a divisional patent application.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 5 and 9 were rejected under 35 U.S.C. § 112, first paragraph, as not being enabled. The rejection does note that the methods of using embryonic stem cells from mice, as was done in the experiments disclosed in the present application, are feasible since embryonic stem cells from mice are available. It is urged that the methods described in the present application are known by those of skill in the art and can be applied to mouse cells and that the claim is enabled as to mouse cells. Furthermore, it is unnecessary to use transgenic animals or animals which have had a gene knocked out in the laboratory. Instead it is possible to use an animal or a person who has been born with a mutation of the elastin gene or genes. For example, persons with SVAS are known to have mutations in an elastin gene. There is no need to "make" these persons, rather several families of persons with SVAS are already known and already studied. Because persons with SVAS are available to be studied and there is no need to "make" persons with a mutant elastin gene it is urged that the claims are enabled for humans as well as for mice. Claims 5 and 9 have been amended to limit them to mice and humans. In view of the amendments to

the claims, it is urged that the claims are enabled and it is requested that the rejection of claims 5 and 9 under 35 U.S.C. § 112, first paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102

Claims 1 and 3 were rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Li et al., *J. Clin. Invest.* 102:1783-1787 (1998). A Declaration by Mark T. Keating, one of the Applicants and one of the authors of the Li et al. publication, is submitted herewith. The Declaration explains the roles of each of the authors of the publication. From the Declaration it is clear that none of the authors other than Dean Y. Li and Mark T. Keating (the Applicants of the present application) contributed intellectually to the preparation of the mutant mice or to the ideas as to how to use the mice. Because the cited reference is a publication of the Applicants it is not to be considered prior art in view of the Declaration of Mark T. Keating. It is requested that this rejection be withdrawn.

Claims 2 and 4 were rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Li et al., Nature 393:276-280 (1998). A Declaration by Mark T. Keating, one of the Applicants and one of the authors of the Li et al. publication, is submitted herewith. The Declaration explains the roles of each of the authors of the publication. From the Declaration it is clear that none of the authors other than Dean Y. Li and Mark T. Keating (the Applicants of the present application) contributed intellectually to the preparation of the mutant mice or to the ideas as to how to use the mice. Because the cited reference is a publication of the Applicants it is not to be considered prior art in view of the Declaration of Mark T. Keating. It is requested that this rejection be withdrawn.

Claims 1-4 were rejected under 35 U.S.C. § 102(b) as being clearly anticipated by Sechler et al. The Sechler et al. publication teaches inserting a mutated rat elastin gene into an otherwise normal mouse. These transgenic mice of the publication are therefore +/+ for the mouse elastin gene, they are not +/- or -/-. They comprise two wild-type mouse elastin genes and a mutated rat elastin gene. Claims 1 and 3 have been amended to make clear that the limitations of the claim refer to mouse genes, not to transgenic genes of other organisms. In view of this amendment, it is asserted that the mice of the Sechler et al. publication do not teach the mice of claims 1 and 3 because the claims require that there either be a mutated mouse elastin gene or no second

elastin gene, but the Sechler et al. mice do have two functioning elastin mouse genes. It is also asserted that the mice of the Sechler et al. publication do not meet the limitations of claims 2 and 4 because these claims require that there be no functioning elastin gene present whereas the mice of the Sechler et al. publication have two functioning elastin genes. In view of the amendments and the above arguments, it is requested that the 35 U.S.C. § 102(b) rejection of claims 1-4 be withdrawn.

Rejections Under 35 U.S.C. § 103

Claims 5, 9 and 10 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Reitamo et al., in view of Li et al. (AE), Su et al., and Li et al. The Li et al. (AE) reference does not qualify as prior art in view of the Declaration by Mark T. Keating submitted herewith and as discussed above in connection with the rejection of claims 1 and 3 under 35 U.S.C. § 102(a) over the Li et al. (AE) publication. Because this 35 U.S.C. § 103(a) rejection relies upon a reference which does not qualify as prior art it is urged that the rejection must fail and it is requested that the rejection be withdrawn.

Claim 6 was rejected under 35 U.S.C. § 103(a) as being unpatentable over Maruyama et al. in view of Sechler et al. The Maruyama et al. reference teaches the administration of an elastase inhibitor to decrease induced pulmonary hypertension in rats. The pulmonary hypertension in these rats was produced by chronic hypoxia which was caused by keeping the rats under hypobaric conditions for 10 days.

Pulmonary hypertension is a completely different condition from essential hypertension. Pulmonary hypertension is concerned with the pulmonary artery and blood pressure between the heart and lungs. Primary or essential hypertension is concerned with blood pressure systemically throughout the body. The causes and treatments of the two conditions are completely separate. Attached to this Amendment are pages from the Merck Manual which discuss both pulmonary hypertension and essential hypertension. Information from these pages of the Merck Manual is discussed in the following paragraphs.

Essential hypertension results from a variety of causes, many of which are unknown, but some essential hypertension results from genetic conditions, some is due to obesity, and some is caused by diabetes. As noted on page 467 of the Merck Manual, in essential hypertension there is increased peripheral resistance throughout the body except in the pulmonary circulation.

Thus, essential hypertension does not concomitantly result in pulmonary hypertension. Treatment of essential hypertension can include loss of weight if the condition is a result of obesity. The condition is also treated by use of diuretics.

Pulmonary hypertension is caused by (1) an irreversible reduction in the vascular bed through disease affecting primarily the blood vessels (e.g., embolization, granulomatoses) or through massive loss of lung tissue, or by (2) arterial hypoxemia which causes pulmonary vasoconstriction. These causes of pulmonary hypertension will not cause essential hypertension.

Because the causes of essential hypertension and pulmonary hypertension are completely separate it is urged that a treatment for one of these diseases would not make obvious a treatment for the other disease. Certainly the hypoxic treatment of the rats by Maruyama et al. would not have resulted in essential hypertension. Therefore, one would not be motivated to use the same treatment to treat rats with essential hypertension as one would use to treat rats with hypoxia induced pulmonary hypertension. Therefore it is urged that the Maruyama et al. reference cannot be used to make obvious the method of claim 6. To make clear that claim 6 is referring to essential hypertension and not to pulmonary hypertension, claim 6 has been amended to insert the term "essential".

In view of the above arguments, it is requested that the rejection of claim 6 under 35 U.S.C. § 103(a) be withdrawn.

In view of the amendments and above arguments, it is submitted that the present claims satisfy the provisions of the patent statutes and are patentable over the prior art. Reconsideration of this application and early notice of allowance are requested. The Examiner is invited to telephone the undersigned to expedite allowance of this application.

Respectfully submitted,

Stephen A. Saxe

Stephen A. Saxe
Registration No. 38,609

Rothwell, Figg, Ernst & Manbeck, P.C.
555 Thirteenth Street, N.W., Suite 701 East Tower
Washington, DC 20004
Telephone: (202) 624-1589
Attorney Docket No.: 2323-127
Dated: 11 May 2000
2323-127.am1